How to Take a Safety-first Approach When Harnessing the Power of HPAPIs

In this article, Mike Avraam at ChargePoint Technology, explores the challenges of handling HPAPIs safely, and discusses how to comply with safety regulations. He explains how the use of next-generation containment technology, including single-use components, can support pharma manufacturers in harnessing the potential of HPAPIs while ensuring the safest possible working environment for employees.

The international high potency active pharmaceutical ingredient (HPAPI) market is growing rapidly. According to Kenneth Research, it is forecast to be worth $33.15 billion by 2025, up from $16 billion in 2016, more than doubling in size in less than 10 years.

This surge has predominantly been driven by the potential these ingredients have for enhancing the efficacy of new drugs for patients. This is particularly the case for treatment of serious or chronic conditions, including therapies for cancer, cardiovascular diseases, and diabetes.

Despite the separate categorisation of HPAPIs, all active pharmaceutical ingredients have pharmacological potency and each can be categorised on a scale of potency from low, to moderate, potent and highly potent. HPAPIs elicit a more targeted pharmacological effect at a lower concentration when compared to traditional alternatives.

In addition, for many potential drug product applications, HPAPIs can receive fast-track designation or accelerated approval to treat the unmet needs of patients often with serious, life-threatening conditions. This means often they pave the way for an expedited route to market, so patients can enjoy the benefits of new, more effective treatments faster.

However, the potent nature of HPAPIs poses many challenges when it comes to their safe handling during the manufacturing process. Careful consideration needs to be taken in the design of production lines, as well as carrying out reliable testing to ensure containment systems effectively minimise the potential for line operatives to come into contact with the materials.

Maintaining Safety

Commensurate with how potentially hazardous HPAPIs are to work with, regulations and guidance surrounding their handling are growing more robust. Regulators are concerned with ensuring a focus on mitigating cross-contamination and that proper facility design is followed for those involved in multi-product operations.

HPAPIs usually are categorised using an occupational exposure band (OEB) strategy, with compounds placed in bands 3, 4 and 5 requiring a variety of special handling and isolation practices. There must also be careful consideration taken in when it comes to understanding and applying the variation of banding criteria from one manufacturer to another.

Limiting handler exposure to these compounds necessitates effective containment technologies. When exposed to higher levels of HPAPIs than what is deemed safe, employees would be at risk of undesired health effects, as the compounds can be carcinogenic, mutagenic, or clastogenic.

Where manufacturing processes involve manual intervention, the process of ensuring an effective containment system within a pharmaceutical environment is especially difficult. Compounding the difficulty of maintaining safety is the necessity for containment solutions to maintain operability and keep productivity of the employees at normal levels.

Regulatory Considerations

There are specific regulations and guidelines that pharmaceutical companies must comply with. COSHH 2002 regulations, for example, call for exposure quantification and worker protections through risk assessments, continuous improvement, collective protection measures, and health and safety precautions.

Smart Factory Technology (SFT) is one way manufacturers can achieve this with the addition of mechanical handling devices to their facilities. By preventing direct handling of product containers or split butterfly valves (SBVs), factories of the future will become less reliant on operator intervention.

SFTs can also monitor the health of production line components and identify where maintenance is required without affecting containment integrity while providing documented audit trails. As a result, it removes the need for manual monitoring of production line equipment, boosting efficiency, removing room for human error and reducing contamination risks.

Containment Technology

To ensure all of these factors are taken care of, from safety to operability, manufacturers must carefully select the correct equipment for their needs, outline processes and procedures, and utilise the appropriate containment technologies. The use of isolators, restricted access barrier systems and SBVs, which function to separate drug products from operators, has grown in recent years. The reason for this is that closed transfer technologies, such as the SBV, are able to limit manual intervention and reduce the risk of cross-contamination.

These types of containment technology have been proven to effectively manage the risk of exposure from airborne dust particulate. This is due to the fact that they have been developed to improve containment for processes where there is a risk of airborne exposure, including during all powder transfer stages. The valves, when integrated with isolators and other process equipment, allow for material to be transferred whilst minimising the risk of it escaping.

Single-use Components

Demands placed on manufacturers by regulations and guidance inevitably increase the need to carry out additional cleaning and validation requirements. This has led many companies involved in HPAPI manufacture to adopt or evaluate the possibility of introducing single-use (SU) technology or systems into the process.

SU technology allows companies to deploy manufacturing solutions that are comparable

in performance but less expensive to operate than traditional systems. In specific use cases, the benefits of SU solutions are the ability to dispose of the materials used rather than employing the labour-intensive cleaning process that traditional systems rely on. The disposability of SU technology is able to reduce cost through various factors, for instance, the initial capital investment is obviously far lower when compared to traditional equipment. However, the ability to reduce washing and cleaning validation activities, alongside the lowered risk of cross contamination, presents other benefits.

It is also now possible to utilise disposable SBV technology within the HPAPI manufacturing environment, which allows for a method of contained powder transfer within a facility, as well as to be used as primary packaging and container closure for transportation to another facility. This enables the manufacturer to eliminate double handling thereby reducing risk while keeping costs down.

Validation Process

Once the handling and containment systems have been selected, it is crucial that they are then tested for efficacy. The International Society for Pharmaceutical Engineering's (ISPE) SMEPAC (Standardised Measurement of Equipment Particulate Airborne Con-centration) guideline is often used as a best practice approach for testing to compare different methodologies. The SMEPAC details the validation methodologies for various technologies and processing equipment, which are focused on determining the efficacy of a system containing particulate matter. It provides methodologies manufacturers can use to derive performance data, which are essential for risk assessments.

Rather than being a list of requirements, the SMEPAC is a guideline but one that is able to provide an effective means of identifying potential risks. What this guideline does not provide, given that the instructions and test methods are conducted in controlled conditions in the laboratory, is an exact replication of how the handling and containment systems will operate in real-world manufacturing. Companies must utilise the data generated during validation to understand this.

Data Assessment and Interpretation

The second stage of the containment technology validation process centres on the containment performance data and its interpretation. It is at this point that manufacturers must identify that testing protocols in the SMEPAC document allow for a degree of inconsistency. Manufacturers can look at containment data and then use it to qualify containment technology; however, it should be noted that variability in the testing methods is possible, and this must be recognised before decisions are made before qualification.

The importance of validating the whole manufacturing process must also be understood, with this involving all of the containment technologies used for the production of the HPAPI. This means that every step where there is a potential for exposure must be validated and a risk assessment carried out. This extends to testing of the impact of operator intervention, especially where a containment device is dependent on operator technique for performance.

Continuous Operational Monitory and Industry 4.0

As should be clear, the requirements for ensuring an effectively contained HPAPI manufacturing process are extensive, time-consuming and complex. Industry 4.0 is changing the pharmaceutical manufacturing process: a continuous monitoring approach with internet-connected equipment that enables real-time evaluation of performance by aligning digital and physical environments.

It is a growing trend to select containment technologies based on their capacity for continuous monitoring and their ability to communicate with other systems on the manufacturing line.

The ability to continuously monitor equipment operational data allows for the revalidation of an existing line, or the validation of lines using duplicate technologies, to be carried out expeditiously. The data generated is also able to indicate potential wear and tear of equipment, which can then be combined with containment testing results to determine a safe operating period or usage cycles for equipment before performance begins to be compromised. This type of containment technology allows preventative maintenance to be carried out preemptively – allowing for the safety and integrity of the manufacturing process for HPAPIs to take place on a more secure level than previously possible.

The innovations happening within the HPAPI manufacturing space are geared to making the process as safe and efficient as possible. The correct choice of containment technology and handling procedures is essential in this process. A securely contained process allows the product to be safely manufactured by employees, which enables the HPAPI to itself to reach the end recipient, the patient, as quickly as possible.

REFERENCES

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